UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	**Civil Action No. 3:16-md-2738-FLW-LHG** **MDL No. 2738**

THIS DOCUMENT RELATES TO ALL CASES

THE PLAINTIFFS' STEERING COMMITTEE'S OMNIBUS BRIEF REGARDING *DAUBERT* LEGAL STANDARD AND SCIENTIFIC PRINCIPLES FOR ASSESSING GENERAL CAUSATION

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The Plaintiffs' Steering Committee ("PSC") submits this omnibus brief in support of its motions to exclude the opinions and testimony of Defendants' experts. This omnibus brief, when read in conjunction with the accompanying expert-specific briefs, will assist the Court with the applicable *Daubert* legal standard for evaluating expert witness general causation opinions and legal and scientific principles pertaining to causal inference. As set forth in the accompanying expert-specific briefs, Defendants' expert witnesses have failed to satisfy the *Daubert* requirements as set forth herein.

I. LEGAL STANDARD FOR ADMISSIBILITY OF EXPERT GENERAL CAUSATION OPINIONS

A. The Admissibility of Expert Testimony Under Fed. R. Evid. 702

The admissibility of expert testimony is determined pursuant to Fed. R. Evid. 702, which incorporates the standards outlined by the United States Supreme Court in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993). Pursuant to this rule, a witness qualified as an expert in "scientific…knowledge" may testify thereto if: "(1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case."[1] As established by the Supreme Court, the trial court acts as a "gatekeeper" to the admission of expert

[1] *Daubert*, 509 U.S. at 592, 597.

scientific testimony under Fed. R. Evid. 702.[2] The trial court must conduct a preliminary assessment "to ensure that any and all scientific testimony . . . is not only relevant, but reliable."[3]

B. Differing and Competing Expert Opinions Are Left for the Jury – The Trial Court Must Only Assess Methodology

The *Daubert* analysis focuses on the methodology underlying an expert's opinion, not the expert's conclusions.[4] *Daubert* requires the proponent of the scientific evidence to show that the expert's conclusion has been arrived at "in a scientifically sound and methodologically reliable fashion," not that the expert's opinion or methodology is beyond reproach.[5] Therefore, the focus of admissibility under *Daubert* is the reliability of the experts' methods, not the correctness of their conclusions.[6] In other words, it is not the trial court's task to decide whether an

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[2] *Id.* at 589.

[3] *Id.*

[4] *Id.* at 595.

[5] *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 85 (1st Cir. 1998); *In re TMI Litig.*, 193 F.3d 613, 665 (3d Cir. 1999) (explaining that plaintiffs "do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are correct, they only have to demonstrate by a preponderance of evidence that their opinions are reliable" (citation omitted)).

[6] *Daubert*, 509 U.S. at 585. *See also Beech Aircraft Corp. v. Rainey*, 488 U.S. 153, 1969 (1988); Fed. R. Evid. 402.

expert's conclusions are *correct.*[7] The trial court is not empowered "to determine which of several competing scientific theories has the best province."[8] As long as the expert's testimony falls within "the range where experts may reasonably differ," then it is up to the jury to decide among the competing views.[9]

The trial court's role under *Daubert* is to ensure that "the expert in the courtroom employs the same level of intellectual rigor that characterizes the practice of an expert in the relevant field."[10] The trial court, as gatekeeper, should require nothing less to protect against junk science from confusing jurors, and to assure that

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[7] *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1318 (9th Cir. 1995) (*Daubert* II) ("[T]he *Daubert* test "is not the correctness of the expert's conclusion but the soundness of his methodology.").

[8] *Milward v. Acuity Specialty Prod. Grp., Inc.*, 639 F.3d 11, 15 (1st Cir. 2011) (internal quotation marks and citations omitted)

[9] *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 153, 119 S. Ct. 1167, 143 L. Ed. 2d 238 (1999); *In re: Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.*, No. 2436, 2016 WL 4039286, at *2 (E.D. Pa. July 28, 2016) ("Fed. R. Evid. 702 and *Daubert* put their faith in an adversary system designed to expose flawed expertise."); *United States v. Mitchell*, 365 F.3d 215, 244–45 (3d Cir. 2004) (citations omitted) ("As long as an expert's scientific testimony rests upon 'good grounds, based on what is known,' it should be tested by the adversary process—competing expert testimony and active cross–examination—rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies."); *In re Urethane Antitrust Litig.*, 166 F. Supp. 3d 501 (D.N.J. 2016) ("in serving the "gatekeeper function" and assessing the reliability of an expert's methodology, the Court must be mindful that in order to be admissible, a scientific method need not be the "best" method or one that is demonstrably correct. "Rather, the test is whether the 'particular opinion is based on valid reasoning and reliable methodology.')

[10] *Kumho Tire Co.*, 526 U.S. at 150–151.

science in the courtroom meets threshold reliability standards.[11] But the converse is also true: the trial court should not impose standards that exceed what is expected and practiced in the expert's field.[12]

C. The Three Basic Inquiries for the Trial Court Under Fed. R. Evid. 702 And Third Circuit Precedent

The Third Circuit has distilled Fed. R. Evid. 702 down to three basic inquiries: qualifications, reliability, and fit.[13]

1) Qualifications

The first requirement mandates that the expert witness must have specialized expertise on the subject matter at hand so they can provide both insightful and relevant testimony.[14] The Third Circuit has held that "a broad range of knowledge, skills, and training [will] qualify an expert."[15]

Whether an expert is the best qualified person to testify on a given matter goes to the weight of the evidence rather than admissibility, and weight decisions should be left to the jury.[16] "However, at a minimum, a proffered expert witness must

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[11] *Daubert*, 509 U.S. at 595.

[12] *Ruiz-Troche*, 161 F.3d at 86.

[13] *JVI, Inc. v. Truckform Inc.*, No. CIV. 11-6218 FLW, 2012 WL 6708169, at *4 (D.N.J. Dec. 26, 2012) (Wolfson, F.) (quotations and citation omitted).

[14] *Pineda v. Ford Motor Co.*, 520 F.3d 237, 244 (3d Cir. 2008).

[15] *Id.* (citation and quotations omitted).

[16] *Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 782 (3d Cir. 1996) ("Because of our liberal approach to admitting expert testimony, most arguments about an expert's

possess skill or knowledge greater than the average layman."[17] "If the expert meets liberal minimum qualifications, then the level of the expert's expertise goes to credibility and weight, not admissibility.").[18] However, while an expert may be qualified in some areas, the expert may not be qualified to testify to specific topics outside his or her area of expertise.[19] Any testimony outside the expert's area of expertise must be stricken. For example, an expert qualified to testify regarding the use of polarized light microscopy (PLM) in the evaluation of talcum powder, but has no expertise in other types of analysis such as Raman spectroscopy or transmission electron microscopy (TEM), may not testify to the strengths or weaknesses of a type of analysis for which they have no experience or expertise.[20]

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qualifications relate more to the weight to be given the expert's testimony than to its admissibility. Thus, witnesses may be competent to testify as experts even though they may not, in the court's eyes, be the 'best' qualified. Who is 'best' qualified is a matter of weight upon which reasonable jurors may disagree.").

[17] *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000).

[18] *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 809 (3d Cir. 1997).

[19] *Surace v. Caterpillar, Inc.*, 111 F.3d 1039, 1056 (3d Cir. 1997); *Buzzerd v. Flagship Carwash of Port St. Lucie, Inc.*, 397 F. App'x 797, 800 (3d Cir. 2010) (affirming exclusion of proffered expert testimony, in part because the witness "articulated no expertise in the field of aerodynamics or air flow"); *see D & D Assocs., Inc. v. Bd. of Educ. of N. Plainfield*, No. CIV.A. 03-1026 (MLC), 2006 WL 755984, at *3 (D.N.J. Mar. 20, 2006) ("If an expert's area of expertise is adjacent to, but not actually encompassing, the subject matter of his testimony, he may be deemed unqualified.").

[20] *See, e.g., Player v. Motiva Enterprises LLC*, No. CIV. 02-3216 (RBK), 2006 WL 166452, at *5 (D.N.J. Jan. 20, 2006) (finding that an expert who was experience in

2) Reliability

Next, the expert's testimony must be reliable.[21] In other words, the expert's opinion must be based on the methods and procedures of science rather than on subjective belief or unsupported speculation; the expert must have good grounds for his or her belief. An assessment of the reliability of scientific evidence under Fed. R. Evid. 702 requires a determination as to its scientific validity.

To determine if an expert's testimony is indeed reliable, the Third Circuit has provided some factors district courts should consider:

> [(1)] whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses.[22]

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appraising uncontaminated properties was unqualified to provide an opinion on the value of contaminated properties).

[21] *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 744 (3d Cir. 1994) ("This does not mean that plaintiffs have to prove their case twice—they do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of evidence that their opinions are *reliable*." (emphasis in original) (italics added)). "[A]n expert is permitted wide latitude to offer opinions, including those that are not based on firsthand knowledge or observation." *Daubert*, 509 U.S. at 592.).

[22] *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 405 (3d Cir. 2003) (citation omitted).

The Third Circuit has explained that this list is non-exclusive and trial courts do not need to apply each factor in every single case.[23] In addition, reviewing these factors is also not a simple analysis and a tally of how many of them end up in a party's favor.[24] Rather, in determining whether to admit an expert's opinion, a trial court must thoroughly assess "whether the 'particular opinion is based on valid reasoning and reliable methodology.'"[25] Finally, the trial court does not have to focus on the conclusions the expert's methodologies create because that is a job for the jury.[26]

Additionally, "[w]here there are other factors that demonstrate the reliability of the expert's methodology, an expert opinion should not be excluded simply

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[23] *Elcock*, 233 F.3d at 746.

[24] *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 152 (3d Cir. 1999) ("In this regard, a party seeking to exclude (or to admit) expert testimony must do more than enumerate the factors from *Daubert* (and the additional ones from *Paoli*, discussed below) and tally the number that are or are not met by a particular expert's testimony.").

[25] *See Oddi v. Ford Motor Co.*, 234 F.3d 136, 145–46 (3d Cir. 2000) (citation omitted).

[26] *See Kannankeril*, 128 F.3d at 807 ("Our inquiry focuses on principles and methodology and not on the conclusions they generate. The analysis of the conclusions themselves is for the trier of fact when the expert is subjected to cross-examination.") (citations omitted); *In re Actos (Pioglitazone) Prod. Liab. Litig.*, 2014 WL 60384, at *8 (W.D. La. Jan. 7, 2014) ("an expert can and does exercise his or her judgment and if he or she gives reasons for that decision and a full explanation for those choices, disagreement with those choice becomes a matter for the trier of fact.").

because there is no literature on point."[27] Furthermore, the method used by the expert does not always have to be correct. The method just needs to be reliable.[28]

The expert, however, must have good grounds for his or her opinion.[29] Courts in the Third Circuit should not strictly apply this reliability requirement.[30] A trial court cannot exclude a novel method of expert testimony so long as the method the expert employs and its application of that method are reliable.[31] Whether or not a court should admit an expert's opinion, depends on "whether the 'particular opinion is based on valid reasoning and reliable methodology.'"[32] And if a court believes

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[27] *Schneider ex rel. Estate of Schneider*, 320 F.3d at 406.

[28] *Pineda*, 520 F.3d at 247 ("While a litigant has to make more than a *prima facie* showing that his expert's methodology is reliable, we have cautioned that the evidentiary requirement of reliability is lower than the merits standard of correctness.") (citations and quotations omitted); *see also Heller*, 167 F.3d at 152 ("Put differently, an expert opinion must be based on reliable methodology and must reliably flow from that methodology and the facts at issue—but it need not be so persuasive as to meet a party's burden of proof or even necessarily its burden of production."); *see also Kannankeril*, 128 F.3d at 807.

[29] *Schneider ex rel. Estate of Schneider*, 320 F.3d at 404 ("[T]he expert must have good grounds for his o[r] her belief.") (quotations omitted).

[30] *United States v. Velasquez*, 64 F.3d 844, 849–50 (3d Cir. 1995) ("We have cautioned, however, against applying the reliability requirement too strictly, explaining that the reliability requirement must not be used as a tool by which the court excludes all questionably reliable evidence. The ultimate touchstone of admissibility is helpfulness to the trier of fact.") (quotations and citation omitted).

[31] *Heller*, 167 F.3d at 153 ("[T]he district court could not exclude the testimony simply because the conclusion was 'novel' if the methodology and the application of the methodology were reliable.") (citation omitted).

[32] *Oddi*, 234 F.3d at 145–46 (citation omitted).

that the expert's opinion does not make sense based on the data in the case, it can properly exclude it.[33]

Focusing on extremely limited evidence, or ignoring the totality of available relevant scientific proof, renders an expert opinion unreliable and scientifically unsound.[34] There is significant support across the country finding expert testimony unreliable if the expert fails to consider contrary evidence. "An expert's opinion may be unreliable if he fails to account for contrary scientific literature and instead '**selectively chooses his support** from the scientific landscape.'"[35]

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[33] *Id.* at 146 ("A court may conclude that there is simply too great a gap between the data and the opinion proffered.") (citations and quotations omitted).

[34] *In re Neurontin Mktg. & Sales Practices Litig.*, 04-CV-10739-PBS, 2011 WL 3852254, at *34 (D. Mass. Aug. 31, 2011), aff'd, 712 F.3d 21 (1st Cir. 2013) (excluding expert's testimony where it was found that the expert "reache[d] his opinion by first identifying his conclusion . . . and then cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion." (citing *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007) (emphasis added)); *Yates v. Ford Motor Co.*, 113 F. Supp. 3d 841, 858 (E.D.N.C. 2015); *see also In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 449 (E.D. Pa. 2014) (finding expert's opinion not reliable or scientifically sound because the expert failed to account adequately for contrary evidence (citing *In re Avandia Mktg.*, No. 2007-MD-1871, 2011 U.S. Dist. LEXIS 479, at *9 (E.D. Pa. 2011)).

[35] *In re Zoloft*, 26 F. Supp. 3d at 449; *Brill v. Marandola*, 540 F. Supp. 2d 563 (E.D. Pa. 2008); *In re Bextra and Celebrex Marketing Sales Practices and Product Liability Litigation*, 524 F. Supp. 2d at 1176; *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 425 & n. 164 (S.D.N.Y. 2005); *Eghnayem v. Bos. Sci. Corp.*, 57 F. Supp. 3d 658, 676 (S.D.W. Va. 2014) (quoting *In re Rezulin Products Liability Litigation*, 369 F. Supp. 2d at 425 (emphasis added and internal citations omitted) "[I]f the relevant scientific literature contains evidence tending to refute the expert's

"[T]he reliability of an expert's opinion should be seriously questioned when it is shown that the expert formed his or her opinion prior to reviewing scientific evidence, and, thereafter, merely **cherry-picked evidence** favorable to that opinion."[36]

In fact, many courts have identified certain methodological flaws as "red flags" that support exclusion of expert testimony on *Daubert* grounds, in addition to "cherry picking." These include: 1) improper extrapolation; 2) reliance on anecdotal

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theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable."); *see also Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 886 (10th Cir. 2005) (affirming exclusion of expert testimony that failed to account for epidemiological evidence); *Pooshs v. Phillip Morris USA, Inc.*, 287 F.R.D. 543, 546 (N.D. Cal. 2012) ("A methodology may not be reliable if an expert fails to address and exclude alternative explanations for the data on which he bases his findings or rejects studies reporting contrary empirical findings."); *Abarca v. Franklin Cty. Water Dist.*, 761 F. Supp. 2d 1007, 1066 n.60 (E.D. Cal. 2011) ("A scientist might well pick data from many different sources to serve as circumstantial evidence for a particular hypothesis, but a reliable expert would not ignore contrary data, misstate the findings of others, make sweeping statements without support, and cite papers that do not provide the support asserted." (internal citations omitted)); *Rimbert v. Eli Lilly & Co.*, 647 F.3d 1247 (10th Cir. 2011) ("[A]n expert who chooses to completely ignore significant contrary epidemiological evidence in favor of focusing solely on non-epidemiological studies that support her conclusion engages in a methodology that courts find unreliable.").

[36] *In re Seroquel Products Liab. Litig.*, 6:06-MD-1769-ORL-22D, 2009 WL 3806434, at *5 (M.D. Fla. June 18, 2009) ("A scientist who has a formed opinion as to the answer he is going to find before he even begins his research may be less objective than he needs to be in order to produce reliable scientific results." (citing *Perry v. United States*, 755 F.2d 888, 892 (11th Cir. 1985) (emphasis added))); *In re Zoloft*, 26. F. Supp. 3d 461.

evidence; 3) insufficient information about the case; 4) failure to consider other possible causes;[37] 5) lack of testing; and 6) subjectivity.[38]

3) Fit

The last part of the Third Circuit's trilogy regarding admission of expert testimony is whether the expert's testimony fits, which means that it is relevant to the case at bar and will help a juror in reaching their final decision.[39]

II. LEGAL AND SCIENTIFIC PRINCIPLES OF CAUSAL INFERENCE

Applying *Daubert* in phased litigation such as this, the PSC's experts are only required to proffer testimony on the issue of general causation. General causation

[37] *Heller*, 167 F.3d at 156 (finding that an expert's testimony "should not be excluded because he or she has failed to rule out every possible alternative cause of a plaintiff's illness," but should only be ruled out if he or she fails to rule out obvious alternative explanations (emphasis added)).

[38] *Oddi*, 234 F.3d at 158 (3d Cir. 2000) (holding that an expert's *ipse dixit* does not withstand *Daubert's* scrutiny); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 595 (D.N.J. 2002) citing *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L. Ed. 2d 508 (1997) ("nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."); *Montgomery Cty. v. Microvote Corp.*, 320 F.3d 440, 448 (3d Cir. 2003) (citing *Joiner*, 522 U.S. at 146); *In re Gabapentin Patent Litig.*, No. CIV.A. 00-2931, 2011 WL 12516763, at *10 (D.N.J. Apr. 8, 2011); *Hamilton v. Emerson Elec. Co.*, 133 F. Supp. 2d 360, 370 (M.D. Pa. 2001) ("*ipse dixit* is defined in Black's Law Dictionary as 'a bare assertion resting on the authority of an individual.' Black's Law Dictionary 828 (6th Ed. 1990)."); *Holman Enterprises v. Fid. & Guar. Ins. Co.*, 563 F. Supp. 2d 467, 470 (D.N.J. 2008).

[39] *See Schneider ex rel. Estate of Schneider*, 320 F.3d at 404 ("[R]ule 702 requires that the expert testimony must fit the issues in the case.).

exists when a substance is capable of causing a disease. In contrast, specific causation exists when exposure to an agent caused an individual plaintiff's disease.[40]

If an exposure to a talcum powder product is capable of causing ovarian cancer in susceptible humans, the general causation requirement is met; it is not necessary that the exposure cause ovarian cancer in all, or most, people. By way of analogy, it is accepted that tobacco smoke causes lung cancer, even though many long-term smokers do not develop lung cancer.

A. Causal Inference is a Matter of Judgement

Scientists recognize that determining causal probability should not be regarded as an experimental or epidemiological result. Rather, it is a "judgment" made about the totality of experimental or epidemiological data.

"Drawing causal inference . . . requires judgment and searching analysis based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa."[41] As this judgment is a scientific determination, it can evolve "as

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[40] *Magistrini*, 180 F. Supp. 2d at 590. *See also In re Zoloft (Sertralinehydrochloride) Prod. Liab. Litig.*, 176 F. Supp. 3d 483, 491 (E.D. Pa. 2016); *see also Leake v. United States*, 843 F. Supp. 2d 554, 558 (E.D. Pa. 2011) ("In toxic tort cases, a plaintiff must demonstrate that the substance at issue is capable of causing the observed harm (general causation), and that the substance actually caused the harm suffered by the plaintiff (specific causation).") (citations and footnote omitted); Restatement (Third) of Torts: Liability for Physical and Emotional Harm [hereinafter Restatement] § 28 cmt. c(3) (2010) (emphasis added).

[41] *Reference Manual on Scientific Evidence*, Fed. Judicial Ctr. (3d ed. 2011) (hereinafter *Ref. Man.*) at 600.

new evidence develops" because "the scientific enterprise must always remain open to reassessing the validity of past judgments."[42] The judgment of whether to draw a causal inference can lead to disagreement amongst experts in the field.[43] This interpretation of scientific studies "can produce legitimate disagreement among experts, and there is no mechanical procedure for resolving such differences of opinion. In the end, deciding whether associations are causal typically is not a matter of statistics alone, but also rests on scientific judgment."[44]

B. A Causal Inference Requires Examining the Totality of the Evidence and No Single Study Is Intended to Support Causation

Scientists believe that assessing causation requires considering and evaluating the totality of the evidence. "Scientific inference typically requires consideration of numerous findings, which, when considered alone, may not individually prove the contention."[45] This is how science outside of the courtroom functions. Only through

[42] *Id.* at 598.

[43] *See, example e.g., In re Neurontin Mktg., Sales Practices, & Prod. Liab. Litig.*, 612 F. Supp. 2d 116, 149 (D. Mass. 2009) (causation supported by biologic plausibility notwithstanding the "robust debate in the scientific community" regarding the proposed mechanism).

[44] *Ref. Man.* at 222.

[45] *Id.* at 19–20; *see also Milward*, 639 F.3d at 26 (reversing the district court's exclusion of expert testimony based on an assessment of the contribution of individual studies to an assessment of causation and finding that the "weight of the evidence" properly supported the expert's opinion that exposure to benzene can cause acute promyelocytic leukemia).

the accumulation of scientific evidence, may a scientist infer causation. There is simply no definitive check-list or magic formula for making scientific judgments. As explained in the *Reference Manual on Scientific Evidence*:

> It appears that many of the most well-respected and prestigious scientific bodies (such as the International Agency for Research on Cancer (IARC), the Institute of Medicine, the National Research Council, and the National Institute for Environmental Health Sciences) consider all the relevant available scientific evidence, taken as a whole, to determine which conclusion or hypothesis regarding a causal claim is best supported by the body of evidence. In applying the scientific method, scientists do not review each scientific study individually for whether by itself it reliably supports the causal claim being advocated or opposed.[46]

As have numerous other courts, the Third Circuit has endorsed an expert's use of the "weight of the evidence" approach to assessing the "totality" of evidence for evaluating general causation.[47] As detailed in the PSC's *Daubert* submissions, the

[46] *Ref. Man.* A primary source of authority for this brief is the *Reference Manual on Scientific Evidence*, published by the Federal Judicial Center. The Federal Judicial Center is the research and education agency of the federal judicial system. It was established by Congress in 1967 (28 U.S.C. §§ 620-629 (2015)), on the recommendation of the Judicial Conference of the United States, with the mission to "further the development and adoption of improved judicial administration in the courts of the United States." *Id.* at xiii-xvi; *see also* Federal Judicial Center, http://www.fjc.gov (last visited Nov. 15, 2018). The PSC refers to the *Reference Manual* (in addition to case law) throughout this brief because it is designed to assist judges on science issues, including *Daubert.*

[47] *See In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787, 796–797 (2017) (citing *Milward*, 639 F.3d at 17 ("[t]he court treated the separate evidentiary components of [the expert's] analysis atomistically, as though his ultimate opinion was independently supported by each."); *see also Magistrini*, 180 F. Supp. 2d at 607; *In re Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.*, 198 F. Supp. 3d 446, 458 (E.D. Pa. 2016); *In re Phenylpropanolamine*

PSC's experts base their general causation opinions on multiple lines of scientific evidence, including, but certainly not limited to epidemiologic evidence.

To better aid scientists in their quest to infer causation, Sir Austin Bradford Hill suggested various factors one could consider to infer causation from association.[48] Hill proposed that consideration of nine "viewpoints" would assist scientists to assess causal relationships.[49] These guidelines are "employed only after a study finds an association to determine whether that association reflects a true causal relationship."[50]

(PPA) Prod. Liab. Litig., 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003) (rejecting defense *Daubert* challenges which "isolate these sources [of evidence] rather than considering the whole"); *Alexander v. Honeywell Int'l, Inc.*, No. 1:17 CV 504, 2018 WL 4220628 (N.D. Ohio Sept. 5, 2018); *In re Seroquel Prod. Liab. Litig.*, 2009 WL 3806435; *McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, No. 2:10CV143, 2014 WL 814878 (W.D. Pa. Feb. 27, 2014); *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291 (N.D. Fla. 2018); *Waite v. AII Acquisition Corp.*, 194 F. Supp. 3d 1298 (S.D. Fla. 2016).

[48] Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. Royal Soc'y Med. 295 (1965), see attached as **Exhibit A**; David E. Lilienfeld, et al., FOUNDATIONS OF EPIDEMIOLOGY 263-266 (3d ed. 1994) (further explaining Bradford-Hill criteria), see attached as **Exhibit B**.

[49] *Id.* The nine viewpoints are: strength or frequency of the association; the consistency of the association in varied circumstances; the specificity of the association; the temporal relationship between the disease and the posited cause; the dose response curve between them; the biological plausibility of the causal explanation given existing scientific knowledge; the coherence of the explanation with generally known facts about the disease; the experimental data that relates to it; and the existence of analogous causal relationships. *Ref. Man.* at 600.

[50] *Id.* at 598-99.

The Third Circuit has endorsed the use of the Hill guidelines as a generally reliable methodology.[51] Numerous legal authorities recognize that the Bradford-Hill criteria require evaluation of all the evidence, with no one factor being dispositive.[52] "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines. One of more factors may be

[51] *See Gannon v. United States*, 292 F. App'x 170, 172–73 (3d Cir. 2008); *In re Zoloft*, 858 F.3d at 796 (citing *Milward*, 639 F.3d at 17) (Bradford Hill criteria is "neither exhaustive nor a necessary list); *see also In re Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, No. CIV.A. 08-08, 2013 WL 1558690, at *2 (D.N.J. Apr. 10, 2013); *In re Tylenol (Acetaminophen) Marketing, Sales Practices, and Products Liability Litigation*, 198 F. Supp. 3d at 455; *In re Avandia Marketing, Sales Practices and Products Liability Litigation*, 2011 WL 13576, at *3 ("Bradford-Hill criteria are used to assess whether an established association between two variables actually reflects a causal relationship.")

[52] *See Magistrini*, 180 F. Supp. 2d at 593 ("[O]ne or more of the factors may be absent even where a causal relationship exists and ... no factor is a *sine qua non* of causation); *In re Fosamax (Alendronate Sodium) Products Liability Litigation*, 2013 WL 1558690, at *4 (denying motion to preclude plaintiffs' expert on general causation because, as here, the expert considered the Bradford Hill factors, and the criticisms went to the weight, not admissibility of the testimony, concluding, "Defendant is free to address these issues on cross-examination..."); *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 26 F. Supp. 3d at 463 (An expert need not consider or satisfy all criteria in order to support a causal inference."); *Milward*, 639 F.3d at 18; *see also* Carl F. Cranor et. al., *Judicial Boundary Drawing and the Need for Context-Sensitive Science in Toxic Torts After Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 16 VA. ENVTL. L.J. 1, 42–49 (1996) (explaining Hill's criteria are not rules but considerations for arriving at best explanation of evidence), attached as **Exhibit C**; Sheldron Krimsky, *The Weight of the Scientific Evidence in Policy and Law*, 95 AM. J. PUBLIC HEALTH S129, S129 (2005) (weight-of-the-evidence methodology mandates that "all scientific evidence that is relevant to the status of a causal hypothesis is taken into account."), attached as **Exhibit D.**

absent even when a true causal relationship exists."[53] Hill himself rejected "hard-and-fast rules of evidence that must be obeyed before we accept cause and effect."[54] As the Restatement explains: "No algorithm exists for applying the Hill guidelines to determine whether an association truly reflects a causal relationship or is spurious."[55] Rather, the Bradford-Hill criteria reflects a "weight of the evidence" approach that involves exercising scientific judgment to arrive at the best explanation, taking into account "all of the relevant available evidence."[56]

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[53] *Ref. Man.* at 600.

[54] Hill in fact concluded:

> What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more likely than cause and effect?

Hill, *supra*, at 299.

[55] *Restatement Third* § 28 cmt. c(3).

[56] *Milward*, 639 F.3d at 23.

C. Both Epidemiologic and Toxicologic Studies Have Value

To determine the effect of an agent in humans, observational studies have some limitations that *in vitro* studies and toxicology models based on live animal studies can overcome.[57]

In vitro studies or studies in cell culture may be conducted and are an important part of the totality of the evidence and the determination of general causation.[58] According to the *Reference Manual,* "the criteria of reliability for an in vitro test include the following: (1) whether the test has come through a published protocol in which many laboratories used the same in vitro method on a series of unknown compounds prepared by a reputable organization (such as the National Institutes of Health (NIH) or the International Agency for Research on Cancer (IARC)) to determine if the test consistently and accurately measures toxicity . . . and (3) whether the test is predictive of in vivo outcomes related to the same cell or target organ system.[59]

Animal studies may also be conducted as actual experiments with researchers exercising total control over study conditions, including agent exposure and subject

[57] *Ref. Man.* at 563-564.

[58] *Id.* at 623, 674.

[59] *Id.* at 649.

participation.[60] Animal studies can avoid the issue of confounding and do not have the same ethical considerations required of studies in human populations.[61] Animal studies also have limitations in that their results cannot always be extrapolated to human populations and the agent dosing used in animal studies does not always translate to human exposure.[62] While not always a perfect solution, "animal studies often provide useful information about pathological mechanisms and play a complementary role to epidemiology by assisting researchers in framing hypotheses and in developing study designs for epidemiologic studies."[63]

Generally speaking, if results from both epidemiologic and toxicologic studies have been produced, "no universal rules exist for how to interpret or reconcile them."[64] However, both can be considered—"careful assessment of the methodological validity and power of the epidemiologic evidence must be undertaken, and the quality of the toxicologic studies and the questions of interspecies extrapolation and dose–response relationship must be considered."[65]

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[60] *Id.* at 563.

[61] *Id.*

[62] *Id.*

[63] *Id.*

[64] *Id.* at 564.

[65] *Id.* at 564-565.

In this litigation, pathology evidence, animal studies, research on biologic mechanisms, *in* vitro tissue studies and epidemiologic research all demonstrate the carcinogenic effect of exposure to talcum powder when applied to the genital area. According to the *Reference Manual*, when this is the case, "an expert's opinion about causation in a particular case is much more likely to be true."[66]

D. Basic Principles of Epidemiology

Basic principles of epidemiology are at issue in assessing general causation under *Daubert*. *Daubert* motions will use terms like "relative risk," "statistical significance," "confidence intervals," "sample size," "power," "bias," "chance," "confounding," and "association." Understanding these concepts is critical to properly interpret the human epidemiologic studies, the causation evidence in this case and the *Daubert* motions. These concepts and their implications are frequently misunderstood particularly in products liability litigation. To assist this Court, the PSC has set forth below a brief overview of basic principles of epidemiology.

1) Epidemiology Relies Largely on Observational Studies

Epidemiology examines the "incidence, distribution, and etiology of disease."[67] Researchers are ethically prevented from knowingly exposing people to an agent suspected to be harmful. Accordingly, based on well-over a decade of

[66] *Id.* at 674.

[67] *Id.* at 551.

medical literature, it is clear that talcum powder is viewed as a potential cause of ovarian cancer. Therefore, the epidemiologic studies pertaining to general causation in this case are necessarily "observational.[68] Another relevant concept, particularly with clinical medicine, is that of "risk factor." The National Cancer Institute defines a risk factor as "something that increases the chance of developing a disease." A cause and effect relationship exists for a risk factor when a plausible mechanism can be identified.[69] The perineal use of talcum powder is frequently reported in the medical literature as a risk factor for epithelial ovarian cancer.[70]

In an observational study, "the investigator identifies a group of subjects who have been exposed [to an agent] and compares their rate of disease… with that of an unexposed group."[71] The most common types of observational studies are cohort

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[68] *Id.* at 555–56.

[69] Vitonis, Allison F., Linda Titus-Ernstoff, and Daniel W. Cramer. 2011. "Assessing Ovarian Cancer Risk When Considering Elective Oophorectomy at the Time of Hysterectomy." *Obstetrics and Gynecology* 117 (5): 1042–50. https://doi.org/10.1097/AOG.0b013e318212fcb7, attached as **Exhibit E.**

[70] Hunn, Jessica and Gustavo C. Rodriguez. 2012. "Ovarian Cancer: Etiology, Risk Factors, and Epidemiology." Clinical Obstetrics and Gynecology 55 (1): 3–23, attached as **Exhibit F**; Mallen, AR, MK Townsend, and SS Tworoger. 2018. "Risk Factors for Ovarian Carcinoma." Hematology/Oncology Clinics of North America, attached as **Exhibit G;** Park, Hyo K., Joellen M. Schildkraut, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa Bondy, Sydnee Crankshaw, et al. 2018. "Benign Gynecologic Conditions Are Associated with Ovarian Cancer Risk in African-American Women: A Case–Control Study." Cancer Causes & Control, September., attached as **Exhibit H.**

[71] *Ref. Man.* at 556.

studies and case-control studies.[72] "The difference between cohort studies and case-control studies is that cohort studies measure and compare the incidence of disease in the exposed and unexposed ("control") groups, while case-control studies measure and compare the frequency of exposure in the group with the disease (the "cases") and the group without the disease (the "controls")."[73]

2) Study Results Are Evaluated for the Existence of an Observed Association

"An association between exposure to an agent and disease exists when they occur together more frequently than one would expect by chance."[74] A causal relationship is one possible explanation for an observed association between an exposure and a disease. However, a causal relationship is just one of several possible explanations for an observed association that must be considered in a search for the most likely explanation. Expressing and interpreting the existence and magnitude of an association involves the concepts of "relative risk," and "odds ratio."[75] Each of these measurements of association examines the degree to which the risk of disease increases when individuals are exposed to an agent."[76]

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[72] *Id.*

[73] *Id.* at 557.

[74] *Id.* at 662.

[75] *Id.* at 566.

[76] *Id.*

3) Study Results are Evaluated for Strength of Association

The strength of the association between an agent and a disease can be expressed using the relative risk ("RR") approach.[77] "It is defined as the ratio of the incidence rate […] of disease in exposed individuals to the incidence rate in unexposed individuals." [78] For example, when the relative risk is expressed as 3.0, the exposed group is at three times the risk of disease as the unexposed group.[79] The "odds ratio" (OR) also quantifies the magnitude of an association.[80] It is similar to the relative risk and is used to approximate the relative risk in a case control study when the disease under investigation is rare.[81] The higher the relative risk, the greater the likelihood that the relationship is causal.

As long as the relative risk exceeds 1.0, there is no minimal threshold for a causal relationship. "While strength of association is a guideline for drawing an inference of causation from an association…, there is no specified threshold required."[82] "If the relative risk is greater than 1.0, the risk in exposed individuals is greater than the risk in unexposed individuals. There is a positive association

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[77] *Id.* at 566.

[78] *Id.*

[79] *Id.* at 567.

[80] *Id.* at 568.

[81] *Id.*

[82] *Id.* at 611, n.186.

between exposure and disease which could be causal."[83] There are a number of well-established causal relationships, where the magnitude of the risk is between 1.0 and 2.0. The magnitude of risk for passive smoking and lung cancer and between smoking and heart disease are well-known examples.[84]

4) Study Results Are Evaluated for the Role of Chance, Bias and Confounding

A false or spurious association can result from three general sources: chance (or random error), bias, and confounding.[85] Before a causal inference may be drawn about an association, the likely existence and impact of these sources must be considered.[86]

Bias can lead to an invalid outcome in epidemiologic studies, and "may arise in the design or conduct of a study, data collection, or data analysis."[87] Bias can amplify, minimize, or hide an association.[88]

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[83] *Id.* at 567.

[84] For example, the relative risk for familiar, established carcinogens are: hormone replacement therapy has a relative risk 1.3 for breast cancer; second-hand tobacco smoke has a relative risk of 1.3 for lung cancer; intermittent sun exposure has a relative risk of 1.6 for melanoma; and benzene has a relative risk of 1.5 for leukemia.

[85] *Id.* at 572.

[86] *Id.*

[87] *Id.*

[88] *Id.*

Confounding "occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and outcome of interest."[89] For a factor to be a confounder for talc and ovarian cancer, it would have to be associated with both the use of talcum powder and the risk for ovarian cancer.[90] "When they can be identified, confounders should be taken into account."[91]

When an association is observed in a study's results, epidemiologists employ statistical techniques to estimate the likelihood that the association is due to chance.[92] Statistical tests, including the calculation of p-values and confidence intervals, are used to evaluate the likelihood that an observed association resulted from chance or random error. "Sometimes the study findings, merely by chance, do not reflect the true relationships between agent and outcome." Any study can be "subject to the play of chance."[93]

There also is a relationship between sample size and the role of chance. A study needs to have a large enough sample size (the number of study participants or power); "by enlarging the sample size … researchers can … reduce the chance of

[89] *Id.* at 591.

[90] *Id.*

[91] *Id.* at 593.

[92] *Id.* at 575.

[93] *Id.*

random error in their results."[94] Statistical tests, including the calculation of p-values and confidence intervals, are used to evaluate the likelihood that an observed association resulted from random error.

P-values are used to determine the likelihood that the observed association occurred due to chance.[95] It "represents the probability that an observed positive association could result from random error even if no association were in fact present. Thus, a p-value of .1 means that there is a 10% chance that values at least as large as the observed relative risk could have occurred by random error, with no association actually present in the population."[96]

For a study's results to be deemed "statistically significant," epidemiologists have historically used a standard that the p-value must fall below a selected significance level (or alpha).[97]

The typical significance level used is .05, where "the probability is 5% of observing an association at least as large as that found in the study when in truth there is no association."[98]

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[94] *Id.* at 576.

[95] *Id.*

[96] *Id.*

[97] *Id.* at 575.

[98] *Id.* at 577.

Finding of an increased risk should not be ignored simply because it did not reach statistical significance, especially when the risk is repeated in different studies. Results that are not statistically significant may be compatible with substantial effects.[99] As noted by one district court citing the epidemiology textbook by Dr. Kenneth Rothman, a "p value cannot provide evidence of lack of an effect."[100] "Observational studies can produce legitimate disagreement among experts, and there is no mechanical procedure for resolving such differences of opinion. In the end, deciding whether associations are causal typically is not a matter of statistics alone, but also rests on scientific judgment,"[101] and requires consideration of all lines of evidence.

a. <u>Statistical Significance is Frequently Misunderstood</u>

In a causal analysis, a study should be included in the consideration even if its results were not statistically significant. "The notion that only when data demonstrates 'statistical significance' do epidemiologists draw inferences about observed associations between suspected risk factors and medical conditions is

[99] *Id.* at 579.

[100] *In re Phenylpropanolamine (PPA) Prod. Liab. Litig*, 289 F.Supp.2d at 1243 (*citing* Rothman, *Epidemiology, An Introduction* at 117).

[101] *See also*, Rothman, K, *Six Persistent Research Misconceptions*, J Gen Intern, Med 29(7); 1060-4 (2014) ("Significance testing has led to far more misunderstanding and misinterpretation than clarity in interpreting study results."), attached as **Exhibit I.**

mistaken."[102] "The term 'statistical significance' could be expunged from the lexicon of the epidemiologist with no loss; accordingly it should not be allowed to assume an importance or role in law beyond its use as an epidemiologist tool."[103] As Hill himself pointed out in 1965 when discussing this very issue: "No formal tests of significance can answer [cause and effect] questions."[104]

As was recently pointed out in an editorial signed by over 800 academics which accompanies 43 articles in the Journal *American Statistician:*

> Let's be clear about what must stop. [W]e should never conclude there is 'no difference' or 'no association' just because a P value is larger than a threshold such as 0.05 or, equivalently, because a confidence interval includes zero. Neither should we conclude that two studies conflict because one had a statistically significant result and the other did not."[105]

b. Confidence Intervals Provide the Probable Range of Risk Estimates

When interpreting a study's results, epidemiologists consider the confidence interval. This can be important in assessing whether the results of several studies are consistent, *i.e.*, when the confidence intervals overlap at say, 20%, they are consistent with a 20% increased risk even if one result is statistically significant and

[102] Rothman Amici Brief at 3.

[103] *Id.* at 4.

[104] Hill, *supra* at 299.

[105] Amrhein, et al., *Scientists Rise Up Against Statistical Significance*, NATURE 567, 305-307 (March 2019), attached as **Exhibit J.**

another is not.[106] As noted in the PSC's other briefing, this concept is relevant to assessing the consistency of several talcum powder human epidemiologic studies. A confidence interval is a range of values consistent with a study's results. "If a 95% confidence interval is specified, the range encompasses the results we would expect 95% of the time if samples for new studies were repeatedly drawn from the same population."[107]

c. A Study's Power Reflects the Likelihood of an Association Being Statistically Significant

Statistical significance and power are inter-related concepts. "[A] large enough sample of individuals must be studied if the study is to identify a relationship between exposure to an agent and disease that truly exists."[108] "The power of a study is the probability of finding a statistically significant association of a given magnitude (if it exists) in light of the sample sizes used in the study."[109] The power of a study depends on several factors: the sample size; the level of alpha (or statistical

[106] *Id.* at p. 306 (Using non-significant 1.2 or 20% example: "It would be ludicrous to conclude that the statistically non-significant result showed "no association" when the interval estimate included serious risk increases.").

[107] *Ref. Man.* at 580.

[108] *Id.* at 576.

[109] *Id.* at 582.

significance) specified; the background incidence of disease; and the specified relative risk that the researcher would like to detect."[110]

d. Confounding as a Source of Error in Epidemiologic Studies

The issue of confounding may be raised by the Defendants in its *Daubert* motions. "Confounding occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and outcome of interest."[111]A confounder must meet this definition: "a confounder is both a risk factor for the disease and a factor associated with the exposure of interest."[112] Having yellow-tinged finger tips is associated with smoking and lung cancer. Even though having yellow-tinged finger tips is associated with lung cancer, it obviously is not a cause of lung cancer. It fits the classic definition of a confounder because it is associated with the exposure (smoking) and the outcome (lung cancer).

There are accepted techniques for adjusting to account for confounders. The existence of the confounders in a study are not the fault of the investigators as they "reflect the inherently 'uncontrolled' nature of exposure designations in observational studies."[113] "It is…necessary to keep [the] risk [of confounding] in

[110] *Id.*

[111] *Id.* at 591.

[112] *Id.*

[113] *Id.* at 593.

perspective. Often the mere possibility of uncontrolled confounding is used to call into question the results of a study. […] The critical question is whether it is plausible that the findings of a given study could indeed be due to unrecognized confounders."[114]

Some bias, like recall bias, are more common with one kind of study design (case-control); and other biases, like "misclassification bias" are more common with others (cohort). Therefore, it is important that each observational study be evaluated individually and not on the basis of any so-called "hierarchies" or "pyramids" that presume one study design generally has more value than another generally.[115]

E. The Law Related to Epidemiology and General Causation

Although there is more than substantial evidence based on epidemiologic studies in this case, the Court should not require that expert opinions be supported by epidemiologic studies, because they are not "*per se* required as a condition of admissibility . . . ."[116] Here, multiple robust statistically significant study results

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[114] *Id.*

[115] Rothman at 1060-1061 ("The type of study should not be taken as a guide to the study's validity.").

[116] *In re Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.*, 198 F. Supp. 3d at 454 (while epidemiological studies can be valuable evidence of causation, they are not a pre-requisite for products liability causation expert testimony in this Circuit); *Wolfe v. McNeil-PPC, Inc.*, No. CIV.A. 07-348, 2011 WL 1673805, at *15 (E.D. Pa. May 4, 2011); *Lanzilotti by Lanzilotti v. Merrell Dow Pharm. Inc.*, No. CIV.A. 82-0183, 1986 WL 7832, at *2 (E.D. Pa. July 10, 1986) ("We note also that it has not been declared in this circuit that epidemiological

support causation. Indeed, the observational studies over the past 40 years yield the following which are not in dispute:

- There are 37 observational studies of talcum powder and ovarian cancer: 31 case-control studies (7 hospital based and 24 population based), 2 pooled case-control studies, and 3 cohort studies;[117]
- The overwhelming majority (n=34) of these studies, irrespective of study design, found a positive association (*i.e.*, a hazard ratio > 1), with most showing an association in the range of 1.1-1.7 representing a 10-70% increased risk of ovarian cancer with talcum powder use;[118]
- In a majority of the published studies (n=19), the positive association reported was statistically significant to a p=.05;[119]
- Even in the published studies that were not statistically significant, the vast majority had confidence intervals which overlapped 1.2-1.25, consistent with a 20-25 % increased risk of

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studies are an indispensable element in the presentation of a prima facie drug product liability case, or that such studies must be the sole basis for expert opinion."); *Mazur v. Merck & Co.*, 742 F. Supp. 239, 264 (E.D. Pa. 1990) (same); s*ee also Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 449 (W.D. Pa. 2003) (discussing the value of epidemiological studies); see also *In re Neurontin Marketing, Sales Practices, and Products Liability Litigation*, 612 F. Supp. 2d at 132 ("Epidemiologic studies, while considered to be 'powerful evidence of causation,' are not required to prove causation in a pharmaceutical personal injury case.").

[117] *See* the *Plaintiffs' Steering Committee's Memorandum of Law in Support of its Motion to Exclude the Opinions of Defendants' Epidemiology Experts Karla V. Ballman, PhD, Christian Merlo, M.D., PhD, Gregory Diette, M.D., MHS, & Jonathan Borak, M.D., DABT*.

[118] *Id.*

[119] *Id.*

ovarian cancer seen in the studies which did find a statistically significant association; [120] and,

- In addition, there are numerous published and unpublished meta-analyses of the observational studies. All show a consistent and statistically significant 25-35% increased risk of ovarian cancer.[121]

However, as noted above statistical significance is not required, and a district court should not "read too much" into the issue of the lack of statistical significance" of an individual study.[122] Instead, the focus under *Daubert* should be on whether an inference of causation can be predicated on the "totality" of the evidence.[123]

The ultimate goal in epidemiology is to judge whether an association between an exposure and disease is, in fact, causal.[124] Although association does not equal

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[120] *Id.*

[121] *Id.*

[122] *Milward*, 639 F.3d at 24 (holding that "[t]he court erred in treating the lack of statistical significance as a crucial flaw"); *In re Zoloft.*, 858 F.3d at 793 (declining to state a bright-line rule on whether statistical significance is necessary noting that "a standard based on replication of statistically significant findings obscures the essential issue: a causal connection.").

[123] "The notion that only when data demonstrates 'statistical significance' do epidemiologists draw inferences about observed associations between suspected risk factors and medical conditions is mistaken." Brief for Kenneth Rothman et al., *supra* note 2, at 3. "Indeed, the term 'statistical significance' could be expunged from the lexicon of the epidemiologist with no loss; accordingly, it should not be allowed to assume an importance or role in law beyond its use as an epidemiologist tool." *Id.* at 4.

[124] Bert Black & David E. Lilienfeld, *Epidemiologic Proof in Toxic Tort Litigation*, 52 FORDHAM L. REV. 732, 750 (1984), attached as **Exhibit K.**

causation, "association often does reflect causation."[125] "Deciding whether associations are causal . . . rests on scientific judgment."[126]

F. The Role of Biologic and Toxicological Evidence in Causal Determinations

To assess whether an observed association is causal, science considers whether the association is "biologically plausible."[127] In assessing the biologic evidence however, it is clear that science need not know precisely how an agent causes a disease[128] and the absence of biologic evidence does not prevent science from establishing causation. Indeed, Hill himself noted that while biologic evidence is "helpful," it is a "feature…we cannot demand [because] what is biologically plausible depends on the biologic knowledge of the day."[129]

Thus, the question is not whether the mechanism of effect is "biologically proven," but whether what is known about association makes it "biologically

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[125] *Ref. Man.* at 221, 264.

[126] *Id.* at 222.

[127] Hill, *supra*.

[128] *In re Phenylpropanolamine (PPA) Prod. Liab. Litig*, 289 F. Supp. 2d at 1243 ("Not knowing the mechanism whereby a particular agent causes a particular effect is not always fatal to a plaintiff's claim. Causation can be proved even when we don't know precisely how the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage somehow." *Daubert II*, 43 F.3d at 1314. *See also Daubert*, 509 U.S. at 590 ("Of course, it would be unreasonable to conclude that the subject of scientific testimony must be `known' to a certainty; arguably, there are no certainties in science.") (Emphasis added).

[129] Hill, *supra.* at 298.

plausible" that there is cause-and-effect. Stated another way, epidemiologists are taught that science should consider whether what is known about the biology of the relationship (if anything)— "makes sense":

> **Biological Plausibility:** The basic question here is, does the association make biological sense? Is the association credible based on our understanding of the natural history of the disease or possible pathogenic mechanisms?[130]

In this case, there has been evidence, most of which has been collected from and reported in the peer-reviewed literature that bears on the question of whether it "makes sense" biologically that the statistical relationship between talcum powder and ovarian cancer reported in the observational studies is likely causal. Though that evidence has been described elsewhere, it is summarized below:

- Talcum powder products contain historically known and suspected carcinogens, including asbestos and asbestiform or fibrous talc, heavy metals and certain fragrance chemicals. This evidence is collected from the peer-review literature, internal but contemporaneous testing by both J&J and the mining company (Imerys), the testing of historical talcum powder samples, and J&J's disclosure of aspects of fragrance formulations. Evidence that J&J's talcum powder products contain known or suspected carcinogens has been cited in the epidemiologic and other literature as being biologically plausible evidence supporting a causal inference between talcum powder products and ovarian cancer;

- Talcum powder products incite an inflammatory response and induce reactive oxidative stress, both known to be involved in the process of carcinogenesis. This biological evidence has been

[130] Oleckno, W.A., *Epidemiology: Concepts and Methods* (2008), attached as **Exhibit L**.

cited in the epidemiologic and other literature as being biologically plausible evidence supporting the causal inference between talcum powder products and ovarian cancer;

- Talcum powder products and similar particles have been reported to "migrate" up the female genital tract and have been found pathologically in ovarian tissue. This biological evidence has been cited in the epidemiologic and other literature as being biologically plausible evidence supporting the causal inference between talcum powder products and ovarian cancer.

G. Scientific Certainty is Not the Burden of the Proponent of Expert Testimony

Science does not demand certainty. Likewise, under Third Circuit *Daubert* standards, the Trial Court should not impose "a standard of scientific certainty . . . beyond that which *Daubert* envisions."[131] Plaintiffs also are not required to present evidence that is conclusive or unequivocal. "[I]n epidemiology hardly any study is ever conclusive, and we do not suggest that an expert must back his or her opinion with published studies that unequivocally support his or her conclusions."[132] Science and medicine often do not lead to certainty and the law does not require certainty.[133]

[131] *Ruiz-Troche*, 161 F.3d at 86.

[132] *Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 354 (5th Cir. 2007).

[133] *Milward*, 639 F.3d at 22 (quoting *Primiano v. Cook*, 598 F.3d 558, 565 (9th Cir. 2010)).

IV. CONCLUSION

As set forth above, virtually all observational studies over four (4) decades with multiple different researchers, assessing different populations, and evaluating different study designs demonstrated an increased risk of ovarian cancer with talcum powder use of 25-35%. Most of these associations were statistically significant. This association and increased risk of ovarian cancer was confirmed by the numerous published meta-analyses which showed the same statistically significant risk.

Moreover, there is reliable evidence from the properly conducted and evaluated studies of a dose response. In addition to the observational studies, there are biologically plausible reasons from which the consistent association could be and was determined to be causal. This includes the fact that Johnson & Johnson's talcum powder products have contained known or suspected carcinogens such as asbestos, a fact that is supported by J&J's own testing, the scientific literature, and testing conducted on historical talcum powder samples produced in this litigation.

Furthermore, J&J's talcum powder products can migrate and reach the ovaries with perineal application, and they have been shown to cause inflammation and oxidative stress (both involved in cancer pathogenesis). Importantly, scientists (outside of litigation) applying Bradford Hill have reached the same conclusions using the same methodology employed by the PSC's experts. For example, it was

recently concluded that the observational epidemiology and the biologic evidence "are indicative of a causal effect."[134]

Based on the law set forth above and the arguments set forth in the PSC's *Daubert* motions and in response to Defendants' *Daubert* motions, the Court should grant the PSC's *Daubert* motions, deny Defendants' motions and advance this litigation to its next phase, case-specific pre-trial discovery to prepare for trials.

Respectfully submitted,

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[134] *See*, Health Canada, *Draft Screening Assessment – Talc*, at p. 21 (December, 2018); *see also id.* at p. 15-21 (general causation analysis entitled: "Perineal exposure to talc"), attached as **Exhibit M**.

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